TITLE: Longitudinal analysis of variation in status and diagnostic stability of untreated dry eye disease

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SHORT TITTLE: Longitudinal analysis of untreated dry eye disease status variations

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Dry eye disease (DED) is a complex ocular condition caused by tear film homeostasis disruption, resulting in ocular signs and symptoms [1]. The Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS-II) introduced a diagnostic methodology that considers not only the presence or absence of symptoms and signs, but also accounts for cases of symptoms without obvious signs (Pre-clinical DED) and marked signs without symptoms (Predisposition to DED) [1]. However, there is a lack of well-designed studies that track changes in DED statuses, signs, symptoms, severity, or the natural history of treated and untreated patients. TFOS DEWS-II emphasizes the need for well-designed studies to estimate the natural course of the disease [1]. This study aims to analyse the status variation in untreated DED participants over 4, 6, and 8 years.

For the initial examination, all subjects were referred to the clinic by their medical doctors with a dry eye-related diagnosis. Prospective participants were contacted for a second visit. The entire sample was randomly divided into three groups: 1) 4-year follow-up group, where from the 35 subjects initially offered, 26 participants were recruited (50.9 ±11.0 years at first visit; error between visits = -11.0 ±17.8 days), 2) 6-year follow-up group, where from the 35 subjects initially offered, 15 participants were recruited (46.8 ±11.2 years at first visit; error between visits = -9.5 ±19.5 days), and, 3) 8-year follow-up group, where from the 35 subjects initially offered, 31 participants were recruited (50.1 ± 8.5 years at first visit; error between visits = 1.8 ±18.8 days). Informed consent was obtained from all participants, and the study protocol adhered to the Declaration of Helsinki and was approved by the institution's Ethics Committee.

The TFOS DEWS-II Diagnostic Methodology Subcommittee criteria was employed to assess the status of each participant in both visits, which included: 1) OSDI questionnaire (cut-off ≥13), tear osmolarity (cut-off ≥308 mOsm/L in one eye or inter-eye difference <8 mOsm/L), tear film break-up time (TFBUT, cut-off <10 s), and corneal staining (cut-off, Oxford grade ≥2) [1-3]. All procedures were performed by the same blinded observer, and data were subsequently coded for analysis. Both eyes of each participant were

evaluated [1-3]. Participants were categorized into four groups based on signs and symptoms according to TFOS DEWS-II criteria: No DED, Pre-clinical DED, Predisposition to DED, and DED [1-3]. Due to the categorical nature of the data participants were compared based on their status using a crosstable design in each follow-up group. Fisher's exact test was assessed to analyse the association between statuses, Cramer's V measured the correlation between initial and final diagnoses, and the Wilcoxon test was used to analyse status variation between visits.

In the 4-year follow-up group, the number of cases of No DED and DED remained stable between visits, while Pre-clinical DED cases decreased and Predisposition to DED cases increased (Table 1). Nevertheless, no association was found between status classification across visits (Fisher, $p = 0.557$), no correlation between the initial and final diagnosis (Cramer's V, $p = 0.213$), and no significant differences in status variation between visits (Wilcoxon, $p = 0.783$).

In the 6-year follow-up group, the number of cases of No DED and DED remained relatively stable between visits, while Pre-clinical DED cases increased and Predisposition to DED cases decreased (Table 1). However, no significant association between status classification (Fisher, $p = 0.114$) or differences in status between visits (Wilcoxon, $p = 0.739$) were found. Conversely, there was a correlation between the initial and final diagnosis (Cramer's $V = 0.565$, $p = 0.048$).

In the 8-year follow-up group, the number of cases for all status categories remained relatively stable between visits (Table 1). A significant association in status classification between visits (Fisher, $p < 0.001$), and a correlation between the initial and final diagnosis (Cramer's $V = 0.819$, $p < 0.001$) were found. However, no significant differences in status were observed between visits (Wilcoxon, $p = 0.317$).

The present study aimed to investigate the natural history of the status in untreated DED participants over an extended period. In the 4-year follow-up group, no significant associations were found, suggesting that while some variation could appear in the status,

there was no linear relationship between categories. Additionally, the lack of correlation between the initial and final diagnosis implies that in short periods the disease may exhibit heterogeneity in its progression. However, at the 6-year follow-up, a correlation between the initial and final diagnosis was observed. This indicates that the disease may have shown a tendency towards consistency in its diagnostic profile over a longer period. Nonetheless, the absence of significant differences in status suggests that the disease's overall progression remained relatively stable during this time. Remarkably, the 8-year follow-up revealed significant associations between status classification at both visits and a strong correlation between the initial and final diagnosis. These findings suggest that disease status became more consistent and predictable over time, potentially aiding in prognosis and treatment planning. Nevertheless, the absence of significant differences in status indicates that the disease's overall status had not changed substantially during the studied extended period.

To date, there is a paucity of studies describing the natural progression of untreated DED. Previous reports have proposed a theoretical model outlining three stages of DED development (Initiation, reflex compensation, and loss of compensatory response). This model suggests that the disease may worsen over time without intervention, possibly reaching a plateau at a certain stage . This hypothesis aligns with the present results, where the shorter follow-up group showed unstable or inconsistent outcomes, while the longer follow-up group showed lower significant variation. Previous studies have established an average duration of DED progression (10.5-14.5 years), which is longer than the duration studied here, which may explain the initial inconsistent results [4]. Moreover, prior research has demonstrated the evolution of DED severity and its association with other inflammatory diseases not presented here [5]. In the present study, it has not been assessed the severity of DED participants, however, based on reported symptoms and signs and their "untreated" status, they may presume to be mild to moderate DED, allowing for a regular lifestyle.

Out of the initial 105 participants contacted, only 72 attended the second appointment. The 4- and 8-year follow-up groups had nearly the complete sample, while less than half of the participants in the 6-year follow-up group were recruited, potentially limiting the results for this part of the analysis. It should be noted that age distribution among the groups was relatively similar, a crucial factor to consider, as it could influence the results if not controlled [6]. Furthermore, previous studies have indicated that ethnicity, particularly the Asian population, may impact the disease's progression [7]; the present study has only included Caucasian participants in the analysis.

Overall, this long-term follow-up study indicates that the initial diagnosis of No DED or DED remains stable over time, with potential variation observed in Pre-clinical and Predisposition to DED cases. The results reveal a strong correlation between the initial and final diagnosis. These findings have significant implications for dry eye disease management, emphasizing the need for long-term monitoring and personalized treatment strategies. Further research is required to comprehend the underlying mechanisms driving these changes and validate these findings in larger and more diverse patient populations.

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Declaration of competing interest

The authors do not have any conflicts of interest to disclose.

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			Visit 2						
			No DED	Pre-clinical dry eye state	Predisposition to dry eye	DED	Total (initial diagnostic)	No variation	Variation
Visit 1	4-year follow-up	No DED	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (100.0%)
		Pre-clinical dry eye state	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	2 (7.7%)	0 (0.0%)	2 (100.0%)
		Predisposition to dry eye	0 (0.0%)	0 (0.0%)	3 (60.0%)	2 (40.0%)	5 (19.2%)	3 (60.0%)	2 (40.0%)
		DED	1 (5.6%)	1 (5.6%)	4 (22.2%)	12 (66.7%)	18 (69.2%)	12 (66.7%)	6 (33.3%)
		Total (final diagnostic)	1 (3.8%)	1 (3.8%)	9 (34.6%)	15 (57.7%)		15 (57.7%)	11 (42.3%)
	6-year follow-up	No DED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-
		Pre-clinical dry eye state	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (6.7%)	0 (0.0%)	1 (100.0%)
		Predisposition to dry eye	0 (0.0%)	2 (66.7%)	0 (0.0%)	1 (33.3%)	3 (20.0%)	0 (0.0%)	3 (100.0%)
		DED	0 (0.0%)	0 (0.0%)	2 (18.2%)	9 (81.8%)	11 (73.3%)	9 (81.8%)	2 (18.2%)
		Total (final diagnostic)	0 (0.0%)	2 (13.3%)	2 (13.3%)	11 (73.3%)		9 (60.0%)	6 (40.0%)
	8-year follow-up	No DED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-
		Pre-clinical dry eye state	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (100.0%)
		Predisposition to dry eye	0 (0.0%)	0 (0.0%)	4 (66.7%)	2 (33.3%)	6 (19.4%)	4 (66.7%)	2 (33.3%)
		DED	0 (0.0%)	1 (4.2%)	2 (8.3%)	21 (87.5%)	24 (77.4%)	21 (87.5%)	3 (12.5%)
		Total (final diagnostic)	1 (3.2%)	1 (3.2%)	6 (19.4%)	23 (74.2%)		25 (80.6%)	6 (19.4%)

Table 1. Cross-table of the number of cases between severity status diagnosis in the first and second visit. n = 72. DED: Dry Eye Disease.